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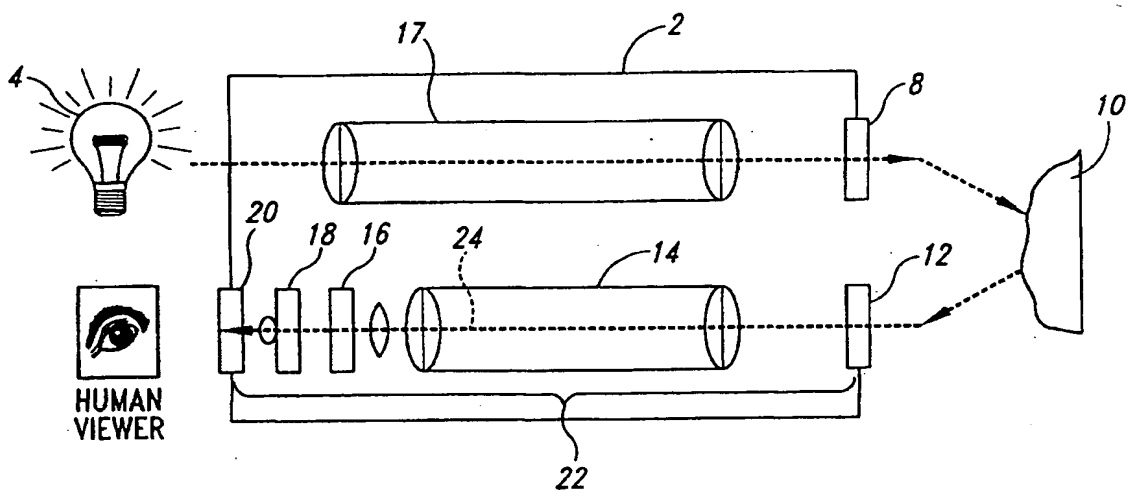


(57) Abstract

Apparatus and methods that permit the direct viewing of induced tissue fluorescence or other response by a human viewer through an endoscope without the need for bulky and expensive auxiliary apparatus such as imaging devices, sensor arrays, analyzing systems and computer hardware and software. The apparatus and methods provide an excitation energy, such as blue light, that is transmitted to the target, and then the endoscope collects the emitted response, which is typically fluorescent light of a wavelength longer than the UV or blue light used to induce the fluorescence. The endoscope then transmits the response through a series of filters in the endoscope and directly to the eye of a human user.

ENDOSCOPES AND METHODS RELATING TO DIRECT VIEWING OF A TARGET TISSUE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to endoscopes for directly viewing a target, such as a target tissue in a human being.

BACKGROUND OF THE INVENTION

Point spectroscopy and spectral imaging of target tissue have been used to assess the condition of tissue in a patient, for example the presence of various illnesses or diseases. Such spectroscopy and imaging have used a variety of different techniques to effect such assessments, including absorbance spectroscopy in transmission and reflectance modes, fluorescence spectroscopy, and Raman spectroscopy (*see, e.g.*, U.S. Patent No. 4,836,203; U.S. Patent No. 5,042,494; U.S. Patent No. 5,062,428; U.S. Patent No. 5,071,416; U.S. Patent No. 5,421,337; U.S. Patent No. 5,467,767; U.S. Patent No. 5,507,287; Mahavedan-Jansen, A. and Richards-Kortum, R., *J. Biomed. Optics I(I)*:31-70 1996; U.S. Patent No. 5,261,410). These techniques have been used in both single and multi-point measurements, and have been used in array spectroscopy to generate images on an imaging device such as a television screen.

A common form of array spectroscopy comprises the use of a color video camera in which a lens system projects an image through optical filters that select a desirable wavelength band or sub-region of the light forming the image, and then projects the image onto an array of sensors. The sensors convert the light into an electrical signal that is proportional to the light incident on a given sensor. The electrical signal can then be stored in a digital or analog format, and/or relayed directly to a device that displays the image, such as a color video monitor. This sort of a system where an image is captured by sensors, converted to electrical or other signals, and then re-created on a viewer (*i.e.*, transduction of the original optical image to a different type of energy and then creation of a new image corresponding to the original image) is known as an imaging device or imager.

The color display monitor recreates an image viewable by a user by converting the electrical signals into optical signals. In this process, a color phosphor that emits light in a narrow wavelength region is stimulated by an amount proportional to the signal originally collected by its corresponding

collect the emanated response light from the target, and transmit the emanated response light through a multi-function filter system in the endoscopes that selectively controls the ratio of the intensities of one or more wavelength bands of the emitted response. In many embodiments, the emanated response light is transmitted directly to the eye of a user without any transduction of the emanated response light. Thus, because several embodiments of the invention allow the user to look directly through the endoscopes to the target, there is no need for a video monitor or other types of transduction imaging devices such as those described above. Several embodiments of the present invention also provide multi-function, variable filter assemblies for use with such endoscopes as well as novel assemblies for varying the efficiency of the filter(s) disposed in the light path of such endoscopes and for identifying pre-selected filter strengths and filter combinations within such assemblies for given diseases.

Accordingly, in certain aspects the present invention provides endoscopes for directly transmitting an image from an *in vivo* target tissue to a user, the endoscope comprising: a body including a proximal end and a distal end, the body being configured to position the distal end proximate to the target tissue; a light emitter proximate to the distal end to direct an illumination light to the target tissue; an eyepiece ocular coupled to the body at the proximal end that is sized to fit a human eye; at least one collection light guide including a collector to receive emanating light from the target tissue and a conductor to conduct the emanating light along at least a portion of a light path to the eyepiece ocular; a wavelength selection filter aligned with the collection light guide to be disposed in the light path, the wavelength selection filter selectively transmitting at least two desired wavelength bands of the emanating light; and a wavelength ratio scaling filter aligned with the collection light guide to be disposed in the light path, the wavelength ratio scaling filter selectively controlling the intensity of at least one of the desired wavelength bands, the wavelength selection filter and the wavelength ratio scaling filter manipulating the emanating light from the target tissue to selectively enhance an image of the target tissue.

In preferred embodiments that relate to this and other aspects of the present invention (which is so for other preferred embodiments unless a given aspect of the invention indicates that such embodiment does not apply to that aspect), the collection light guide transmits the emanating light to the eyepiece, wherein the user is able to directly view the target tissue directly through the eyepiece ocular without a transduction imaging device between the target tissue

configured to position the distal end proximate to the target tissue; means for emitting an illumination light from a location of the body at least proximate to the distal end; means for collecting and conducting an emanating light from the target tissue along a light path to an eyepiece sized to fit a human eye at the proximal end, wherein the means for collecting and conducting the emanating light filters the emanating light to conduct a first specific bandwidth of light at a first intensity and a second specific bandwidth of light at a second intensity to the eyepiece, such that a wavelength of light depicting an image of the target tissue is selectively enhanced.

In still other aspects the present invention provides methods for a user to directly view a target tissue through an endoscope, the methods comprising: a) illuminating the target tissue by emitting illumination light from a distal end of the endoscope to the target tissue under conditions suitable to thereby cause light to emanate from the target tissue to provide an emanating light; b) collecting the emanating light that contacts the distal end of a light collection system maintained in the endoscope; c) conducting the emanating light along a light path from the distal end of the endoscope to an eyepiece ocular at the proximal end that is sized to fit a human eye, wherein such conducting comprises transmitting the emanating light through a wavelength selection filter that selectively transmits at least two desired wavelength bands of the emanating light and through a wavelength ratio scaling filter that selectively controls the intensity of at least one of the desired wavelength bands to provide a filtered light representation of the target tissue; and, d) viewing the filtered light representation of the target tissue through the eyepiece ocular.

In certain preferred embodiments, the target is illuminated by conducting the illumination light from a light source maintained at the proximal end of the endoscope to a light emitter maintained at the distal end of the endoscope via an illumination light guide and then emitting the illumination light to the target tissue. In further preferred embodiments, the illumination light is transmitted through a band pass filter maintained at the distal end of the endoscope, wherein the band pass filter transmits a selected wavelength band of light and blocks other light. The selected wavelength band can be blue light able to induce fluorescence in the target tissue.

In other preferred embodiments, the illumination light emitted from the light emitter consists essentially of a selected wavelength band and the light collection system further comprises a long pass filter disposed in the light path,

disposed at the distal end of the collection light guide and that substantially blocks blue light, a wavelength selection filter disposed in the light path and able to selectively transmit at least two desired wavelength bands of the emanating light, and a wavelength ratio scaling filter disposed in the light path and able to selectively control the intensity of at least one of the desired wavelength bands, and wherein the user is able to directly view the target tissue through the eyepiece ocular without an imaging device between the target tissue and the user.

In some preferred embodiments, the illumination light is conducted from a light source maintained at the proximal end of the endoscope to the light emitter at the distal end of the endoscope via the illumination light guide, and wherein a band pass filter that transmits substantially only blue light is disposed at the distal end of the illumination light guide.

In still more aspects the present invention provides filter assemblies for a scope to transmit an image from an *in vivo* target tissue to a user, comprising: a casing including a proximal end with a first opening to receive a proximal section of the scope, a distal end with a second opening to receive a distal section of the scope, and a transmission passage extending between the first and second openings, the transmission passage being configured to transmit light along a light path from the distal end to the proximal end of the casing; a rotatable housing attached to the casing, the rotatable housing including a knob configured to be gripped by a user and a filter holder positioned in the casing, the filter holder having a plurality of windows; and, at least one filter received in one of the windows, the housing rotating within the casing to position the at least one filter in alignment with the light path for selectively enhancing an image of the target tissue.

In some preferred embodiments, the at least one filter disposed within the at least one wall of the filter assembly is able to transmit at least two discrete desired wavelength bands of the light, and/or the filter assembly comprises at least two of the housings, at least one housing having a wavelength selection filter disposed in the light path that is able to selectively transmit the at least two discrete desired wavelength bands, and at least one housing having a wavelength ratio scaling filter disposed in the light path and able to selectively control the intensity of at least one of the desired wavelength bands.

In other preferred embodiments, the filter assembly further comprises a non-rotatable lens that maintains the sharpness of an image being transmitted along the light path and disposed in the light path within the housing.

Figure 4C is an isometric view of the emission wavelength ratio scaling filter depicted in Figure 4A.

Figure 5 is an exploded isometric view of the emission wavelength ratio scaling filter of Figures 4A-4C, wherein the filter is disposed in-line in the body of an endoscope.

Figure 6 is an isometric view of the emission wavelength ratio scaling filter of Figures 4A-5 enclosed in an in-line housing in an endoscope according to an embodiment of the present invention.

Figure 7 is a side view of a further embodiment of an emission wavelength ratio scaling filter, wherein various strength filters are cascaded to be selectively interposed in a light path.

Figure 8 is an exploded isometric view of one embodiment of an emission wavelength ratio scaling filter as depicted in Figure 7, wherein the varying strength filters are retained in rotatable wheels.

Figures 9A and 9B are graphs illustrating fluorescence spectra from a transplanted rat heart and a control rat heart.

Figure 10 is a schematic drawing of a pulsed xenon flash-lamp source.

Figure 11 is a schematic drawing of a focused continuous wave (CW) arc lamp.

Figure 12 is a schematic drawing of a collimated CW arc lamp.

Figure 13 is a schematic diagram depicting an embodiment of the present invention comprising a system for inducing fluorescence wherein an LED is disposed at the distal end of an endoscope.

Figure 14 is a schematic diagram depicting another embodiment of the present invention comprising an illumination apparatus wherein an LED is disposed at the distal end of an optical viewer.

Figure 15 is an and end view of an array of illumination LEDs disposed around a collection light guide.

Figure 16 is a schematic diagram depicting a side view of an array as set forth in Figure 15.

Figures 17A-17C are graphs depicting the percent transmission of a red-green wavelength selection filter, a red-green wavelength ratio scaling filter having six discrete filters, and a red-green wavelength ratio scaling filter wherein the filtration of the red-green wavelength is continuously variable as a function

ability to control the ratio of the intensities of the wavelength bands permits the user to optimize the effectiveness of his or her assessment of the target.

Turning to a general discussion of the apparatus and methods of the invention, an "endoscope" is a generally tubular device for insertion into a body, typically via canals, vessels, passageways or body cavities for any of a variety reasons, such as diagnostic purposes, the injection or withdrawal of fluids or to keep a passageway open. As used herein, an endoscope is an *in vivo* optical viewer for viewing internal targets (such as internal organs) and includes other such internal, *in vivo* optical viewers such as laparoscopes, fundascopes, colposcopes, otoscopes and surgical microscopes. An endoscope is similar to a catheter, except that generally an endoscope is considered to transmit an image while a catheter does not; for the purposes of the present specification, the term endoscope includes catheter unless otherwise clear from the context. The endoscope is preferably rigid, but can be flexible. The discussion herein regarding endoscopes also generally applies to other types of *in vivo* optical viewers, including viewers for external use such as otoscope-like viewers for examining the skin, unless clear from the context.

The distal end of an endoscope is the end of the endoscope that is inserted into the body and directed to a target tissue; the proximal end is the end of the endoscope that is maintained outside the body, and typically comprises an ocular eyepiece and one or more handles, knobs and/or other control devices that allow the user to manipulate the distal end of the endoscope or devices located at the distal end of the endoscope. As used herein, the distal end of the endoscope includes the distal tip of the endoscope, which is the most distal surface or opening of the endoscope, and the portion of the endoscope adjacent to the distal tip of the endoscope. Endoscopes generally are well known. U. S. Patent No. 5,409,000; U. S. Patent No. 5,409,009; U. S. Patent No. 5,259,837; U. S. Patent No. 4,955,385; U. S. Patent No. 4,706,681; U. S. Patent No. 4,582,061; U. S. Patent No. 4,407,294; U. S. Patent No. 4,401,124; U. S. Patent No. 4,204,528; U. S. Patent No. 5,432,543; U. S. Patent No. 4,175,545; U. S. Patent No. 4,885,634; U. S. Patent No. 5,474,519; U. S. Patent No. 5,092,331; U. S. Patent No. 4,858,001; U. S. Patent No. 4,782,386; U. S. Patent No. 5,440,388. Endoscopes comprising optical probes and methods of analyzing scans using the same are also well known in the art. U. S. Patent No. 5,421,337; U. S. Patent No. 5,507,287; U. S. Patent No. 5,467,767; U. S. Patent No. 5,071,416; U. S. Patent No. 5,042,494; U. S. Patent No. 5,062,428; U. S. Patent No. 4,836,203; U. S.

not maintained at the distal tip, to the proximal end of the endoscope where the light is presented at an eyepiece ocular for direct viewing by a user. Thus, in many aspects of the invention, the light path provides for direct transmission of the image of the target tissue from such tissue to the user without any transduction imaging device interspersed in the light path. Please note, however, that in some embodiments of the present invention a transduction imaging device can be attached to the endoscope for a secondary viewing option of the target tissue, but such transduction imaging device is still not typically maintained within the light path for the purposes of the present invention because such transduction imaging device does not create the image provided in the eyepiece ocular. The eyepiece ocular is a viewing site for the user and is typically a monocular eyepiece, but it can be binocular or a piece of ground glass that functions as a viewscreen or other direct viewing device.

The illumination light guide and the collection light guide can be a single light guide, which means that the same light guide can function as both the illumination light guide and the collection light guide. Alternatively, the illumination light guide and the collection light guide can be separate light guides. In a preferred embodiment, the illumination and/or collection light guides comprise a focusing device at their downstream (*i.e.*, distal end or proximal end, respectively), for example a gradient refractive index (GRIN) lens, a microlens, or a diffractive optic lens. Typically, the light guide can be an optical fiber, fiber bundle, liquid light guide or hollow reflective light guide or lens system, or other pathway suitable for carrying the image of the target from the distal end to the proximal end of the endoscope. The light path can also comprise, or consist of, a hollow air-filled casing, for example in an otoscope or otoscope-like instrument. Each of the illumination light guide and the collection light guide are able to conduct light along at least a portion of its relevant light path. For example, the collection light guide can transmit the emanating light from the distal end to the proximal end of the endoscope; if all filters and optical elements are disposed between the two ends of the collection light guide, then the collection light guide is deemed to conduct the emanating light along the entire light path from the distal end of the endoscope to the ocular eyepiece at the proximal end of the endoscope. On the other hand, if one or more of the filters or other optical elements disposed in the light path are disposed either before or after the collection light guide (*i.e.*, upstream or downstream, respectively), then the collection light guide conducts light along a portion of the light path.

wavelength selection filter blocks out any reflectance (blue or UV) light, thereby transmitting only fluorescent light.

In another preferred embodiment, the wavelength selection filter blocks a substantial portion, and preferably all, wavelengths of light that are within the overlapping photoreceptor response ranges of the human eye. (See Figure 2.) Typically, such filters block from about 530 nm to about 560 nm, and at least one other wavelength band, which second band can vary according to the desires of the user.

Some preferred combinations of illumination light and desired wavelength bands include those wherein the illumination light is blue or UV light that induces fluorescence, the desired first and second wavelength bands are from (a) about 480 nm – 530 nm and (b) about 560 nm - 725 nm or longer, respectively. In another embodiment, for example where the illumination light is UV light such as 380 nm, the desired first and second wavelength bands are from (a) about 400 nm – 440 nm (*i.e.*, blue light) and (b) about 530 nm / 560 nm – to any longer wavelength, respectively; if the illumination light is increased to about 400 nm-405 nm, then the desired first wavelength band (a) is increased to about 420 nm / 440 nm. In another preferred embodiment, the illumination light is about 380 nm – 410 nm and the desired first and second wavelength bands are from (a) about 410 nm – 440 nm and (b) about 480 nm – 520 nm (*i.e.*, from about 440 nm – 480 nm and from about 520 nm and longer are blocked). In another embodiment, known as multi-photon induction of fluorescence and discussed further below, the effective wavelength of the illumination light is the same as discussed above, but the actual wavelength is 2x (or other multiple) the effective wavelength; the desired wavelength bands remain the same.

The wavelength ratio scaling filter selectively controls the ratio of the intensities of the two or more desired wavelength bands that are transmitted by the wavelength selection filter. Typically, the wavelength ratio scaling filter selectively controls the ratio by attenuating or diminishing one or more of the desired wavelength bands. The wavelength ratio scaling filter preferably filters at least a wavelength band of light that is slightly greater in width than the selected desired wavelength band that it is filtering (thus, the wavelength ratio scaling filter preferably acts on a band of light that is "overlapping" relative to the selected desired wavelength band that has been transmitted by the wavelength selection filter). Preferably, the degree that the desired wavelength band is selectively controlled by the wavelength ratio scaling filter can be varied by

preferred combinations comprise filters that enhance the visibility of wavelength bands absorbed by blood (*e.g.*, about 540 nm ± 10 nm and about 580 nm ± 10 nm) for situations where the user desires to find or avoid blood vessels, or combinations that block such wavelengths where absorption by blood is an interference to the desired viewing. Other preferred combinations enhance the visibility of wavelength bands associated with desired photo-activated drugs.

In one preferred embodiment, typically where the present invention comprises a kit, a plurality of different filters/filter assemblies can be readily input and removed from the endoscope, and the invention provides a storage rack or other framework that holds or retains the different filters and/or multi-filter assemblies (such as the filter wheels and disks depicted in Figures 3-8) when they are not in place in the endoscope and/or the plurality of different filters/filter assemblies themselves. The filters/filter assemblies can be identified by identification marks (*e.g.*, labels, etching) attached to or imprinted upon the filters/filter assemblies themselves and/or to dedicated slots or spaces in the rack that are specific for given filters/filter assemblies.

In another preferred embodiment, the present invention provides hand-held *in vivo* optical viewers that can be similar to an otoscope; such a device can be used for either internal or external review of a patient, depending upon the desires of the user. The device can be either battery powered or connected via electrical leads to an external power source. In one preferred embodiment, the device is battery powered by rechargeable batteries that are automatically recharged upon placement of the device into a recharging stand. In a preferred embodiment, this hand-held device comprises light emitting diodes (LED's) at the distal end of the viewer, which LED's emit desired wavelength(s) of light.

Where such a hand-held device is to be used external to the body, the device is preferably used in a darkened room. Alternatively, the distal end of such a viewer can comprise a hollow, substantially tubular extension (which can also house the other components of the *in vivo* optical viewer as discussed herein) that is suitable for contact with the skin or other external surface under investigation. In preferred embodiments, the distal end of such a tubular housing forms an angle relative to the light path such that the *in vivo* optical viewer is held in contact with the skin (or other target site) at an angle other than perpendicular, for example a 45° angle to the skin. This can reduce the amount of reflectance light that enters the light collection system of the viewer. In

As noted above, some preferred methods and apparatus of the present invention comprise the induction and viewing of fluorescence in a target tissue. This is because healthy tissue exhibits a characteristic fluorescence response in reply to excitation with electromagnetic radiation having a wavelength in the ultraviolet to visible light ranges, while the fluorescence response of diseased, injured or otherwise harmed tissue changes relative to the healthy tissue. The illumination or excitation light energy that is transmitted to the target tissue typically comprises light from ultraviolet light through visible light and can induce fluorescence, reflectance or other response in the target tissue. Preferably, the light does not comprise UV light because such light can be harmful to the tissue. Conditions to induce fluorescence in tissue are well known in the art. *See, e.g.*, U. S. Patent No. 4,836,203; U. S. Patent No. 5,042,494; U. S. Patent No. 5,062,428; U. S. Patent No. 5,071,416; U. S. Patent No. 5,421,337; U. S. Patent No. 5,467,767; U. S. Patent No. 5,507,287.

Fluorescence and fluoresce are used herein in their ordinary sense, which includes the emission of, or the property of emitting, electromagnetic radiation, typically in the visible wavelength range, resulting from and occurring after the absorption of the illumination or excitation light that is transmitted to the transplanted tissue. Fluorescence includes fluorescent light produced by either endogenous fluorophores or exogenous fluorophores; exogenous fluorophores include those provided by drugs, chemical labels or other external sources. Autofluorescence is fluorescence from endogenous fluorophores. The fluorescence is collected, or gathered, from the target tissue so that it can be analyzed to provide a target fluorescent image, which means a particular fluorescent image for that particular target tissue.

Fluorescence characteristics that contribute to the changes observable in target tissue undergoing a specific disease state or other condition are affected by the wavelength of excitation, and the concentration, absorption coefficients, scattering coefficients, quantum efficiency, and the emission spectra of the fluorophores inside the tissue. For example, *in vivo* determination of the presence or absence of characteristics of rejection of a target heart preferably includes viewing the endocardium, epicardium, myocardium and/or arterial tissue for the fluorescence characteristics described above, as well as changes in fluorescence characteristics due to physiological changes associated with rejection such as thickening of the endothelium and increase in collagen content.

conditions that are suitable to cause light to emanate from the target tissue. As noted above, such light that emanates from the target tissue is termed "emanating light." A portion of the emanating light contacts the distal end of a light collection system that is maintained in the endoscope, and is then collected or gathered by such light collection system. The light is then conducted along a light path from the distal end of the endoscope to an eyepiece ocular at the proximal end of the endoscope, where the light is available for viewing by a user.

The light is passed through a wavelength selection filter that selectively transmits at least two desired wavelength bands of the emanating light and through a wavelength ratio scaling filter that selectively controls the intensity of at least one of the desired wavelength bands to provide a filtered light representation or image of the target tissue. The filtered light representation is a direct optical representation of the target tissue, as opposed to a spectrograph or other scan of the target tissue. In addition, the filtered light representation or image is a direct image, as opposed to an image created by transduction in an imaging device. The methods then comprise viewing the filtered light representation of the target tissue through the eyepiece ocular without an imaging device between the target tissue and the eyepiece. In preferred embodiments, the target is illuminated by conducting the illumination light through a band pass filter maintained at the distal end of the endoscope, which filter transmits the selected wavelength band of illumination light and blocks other light, for example to eliminate interfering fluorescence derived from the illumination light guide itself. In addition, the emanating light is preferably collected through a long pass filter disposed at the distal end of the endoscope, which long pass filter eliminates unwanted light such as reflectance light from the illumination light.

In another embodiment, the methods, in addition to or in place of certain other steps discussed herein, comprise selecting a particular filter combination (*i.e.*, a particular set of a desired wavelength selection filter and a desired wavelength ratio scaling filter) for a specific purpose by choosing a setting for the filters that is identified by one or more labels or other markings reciting one or more specific diseases or other conditions for which the particular filter combination is appropriate. The particular filter combination that is thus selected can be chosen, for example, by rotating a disk comprising a plurality of desirable filters and having disposed on the side thereof the labels identifying the disease(s) or other condition(s), by turning a knob that is visible to the user has such labels on its top or side, or by selecting the filter or multi-filter holder (such

8 filters out at least substantially all undesired wavelengths of light and transmits the desired bandwidth of light. The location of band pass filter 8 at the distal end is preferred where the illumination light comprises or consists essentially of light that can induce artifacts in the illumination light guide (such as fluorescence from the illumination light guide itself); the band pass filter 8 blocks such artifacts from reaching the target. The illumination light is then directed from band pass filter 8 to tissue 10. Thus, in the embodiment depicted in Figure 1, band pass filter 8 acts as a light emitter for endoscope 2; if no band pass filter is disposed at the distal end of endoscope 2, then the distal end of illumination light guide 7, or an alternative desired optical element (if any) disposed at the distal end of endoscope 2, acts as the light emitter. The light emitter, therefore, can be an active light source that generates the light, or the light emitter can be a passive transmissive element that projects the light.

Upon entering tissue 10 (or other target) the illumination light causes a response in tissue 10, which response is an emanating light comprising reflectance light, fluorescence light, and/or other light-induced responses. In a preferred embodiment, the light source 4 is a blue light excitation source, and the distal end band pass filter 8 transmits only blue light of about the wavelength emitted by light source 4. When the light source 4 is an appropriate light source, fluorescence is induced as the response in target tissue 10. Target tissue 10 then emits its response as emanating light or other electromagnetic energy.

The light emanating from tissue 10 contacts the distal end of light collection system 22, which is maintained in endoscope 2. The emanating light travels along light path 24 through a long pass filter 12 maintained at the distal end of the light collection system 22, which long pass filter, in a preferred embodiment, eliminates reflectance light from the excitation light source 4. Collection light guide 14 then conducts the emanating light to an emission wavelength selection filter 16, which filter 16 selectively transmits at least two desired wavelength bands. The light then continues along light path 24 to wavelength ratio scaling filter 18, which selectively filters, attenuates or decreases at least one of the desired wavelengths that were transmitted by wavelength selection filter 16. The emanating light then continues along light path 24 to eyepiece ocular 20, where the light can be viewed as an image by the eye or eyes of the user.

Figure 2 comprises a graph that depicts the spectral sensitivity curves, or color response, of the cones and rods that are found in the human eye.

holders 202, 202a each have a receiving channel 216, 216a in the superior surface thereof; such receiving channels receive nubs 217, 217a projecting from the inferior surface of threaded filter supports 215, 215a. Thus, as threaded filter supports 215, 215a are moved along threaded projections 210, 210a, their nubs 217, 217a move within receiving channels 216, 216a, thereby causing simultaneous, compensating rotation (*i.e.*, co-angular movement) of filter holders 202, 202a and filters 32, 32a therein.

Turning to Figures 3E and 3F, the co-angularly adjustable assembly of Figures 3C and 3D is depicted in place in an in-line casing 220 disposed within a distal sheath 100 and proximal sheath 106 of an endoscope. The co-angularly adjustable assembly can be attached via a mounting screw that is transmitted through opening 208 in cross-member support 212 and into mounting screw receiving body 214 that is located within in-line casing 220. Preferably, in-line casing 220 comprises a lens 222 at its proximal end (a corresponding lens, not shown, is also preferably disposed in-line at the distal end of in-line casing 220), to maintain the clarity of the image transmitted by the endoscope.

Other methods and apparatus for co-adjusting the filters will be apparent to those of ordinary skill in the art in view of the present specification. By providing such co-adjusted filters, any deflection or other redirection of light path 24 upon passage through a first filter (*e.g.*, filter 32) is corrected for by passage through the second filter (*e.g.*, filter 32a).

Figure 3G is an isometric view of an optical bioptome 2a with the in-line casing 220 housing the wavelength ratio scaling filter described above with reference to Figures 3B-3F. In this embodiment, the optical bioptome has a light source 4, a manipulator 5, a bioptome assembly 9, and an eyepiece 11. One suitable optical bioptome is disclosed in U.S. Patent Application No. 09/039,279, filed on March 12, 1998, which is herein incorporated by reference as set forth above. As set forth above, the casing 220 is attached to a proximal sheath 106 and a distal sheath 100. The light source 4 is attached to an excitation sheath 301. The distal sheath 100 and the excitation sheath 301 join at proximal body section 303. The proximal end of manipulator 5 is attached to the proximal body section 303, and the distal end of the manipulator 5 is attached to a distal body section 305. The illumination light guide 7 (Figure 1) is carried in the excitation sheath 301, proximal body section 303, and the distal body section 305. Similarly, the light collection system 22 is carried in the proximal and distal sheaths 106 and 100, and in the proximal and distal body sections 303 and 305.

comprise a series of identifying marks 107 that identify the strength or other property of a corresponding filter. In preferred embodiments of the invention, as discussed above, specific markings indicate preferred filters for specific disease(s). Such identifying marks can be viewed through opening 108 in proximal housing 104. Alternatively, outer edge 54 of disk 42 can have identifying marks thereon, which can be seen because outer edge 54 extends through a space created by rectangular openings 112 in flattened surfaces 114 of each of distal housing 102 and proximal housing 104.

Figure 6 depicts an isometric view of the assembly of Figure 5 wherein the assembly has been put together. As can be seen, outer edge 54 of disk 42 is available for manipulation by a user, thereby permitting such user to easily turn disk 42 and place a desired filter in light path 24.

Figure 7 is a schematic view illustrating a third embodiment of an adjustable wavelength ratio scaling filter wherein the filters are cascaded. In the figure, light path 24 traverses one or more filters disposed in a line and selectively interspersed into light path 24 to provide a variety of different levels of filtering. For example, in Figure 7, the first filter is a 50% filter 60 that blocks 50% of the selected desired wavelength band, the second filter is a 20% filter 62 that blocks 20% of such light, the third filter is a 10% filter 64 and the fourth filter is a 5% filter 66. These filters can then be interspersed in the light path 24 either singly, all at once or in any desired combination to provide a variety of different levels of filtering. Of course, more or less than four filters can be used at the desire of the user.

Figure 8 is an exploded isometric view illustrating a preferred embodiment of a filter assembly suitable for use with an adjustable wavelength ratio scaling filter having cascaded filters as in Figure 7, wherein the filters are maintained in the sides of a rotatable, substantially circular housing that forms a part of the assembly. In Figure 8, a lower casing 122 has a transmission passage 156 therein that is sized to receive and transmit light path 24. In addition, transmission passage 156 comprises a first chamber 128 and second chamber 130 that are each sized to receive first and second rotatable housings 158, 160, respectively. The rotatable housings 158, 160 are substantially cylindrical, and can be hexagonal or otherwise geometrically shaped, such as other polygons, circles or ovals in cross-section.

Each of the rotatable housings 158, 160 contains therein a plurality of different filters 136, 138 and a corresponding plurality of openings 146

light path 24 enters the distal end 124 of the casing, passes through one of the first filters 136 on a side 137 of the first housing 158 facing the distal end (which filter has been rotated to be in line within light path 124), then the light traverses first lens 132, passes through a first opening 146 in the first rotatable housing 158 facing the proximal end 126, traverses one of the second filters 138 on side 139 of the second rotatable housing 160 facing the distal end 124 (which has also been rotated to be in line within light path 24), then traverses second lens 134, passes through a second opening 146 in the second rotatable housing 160 facing the proximal end 126, and then continues downstream to exit the assembly at proximal the end 126.

In other embodiments, the assembly can comprise only one or more of the rotatable housings (*e.g.*, 3). Additionally, each rotatable housing can comprise three filters and three corresponding openings as described in the figure, or such housings can comprise any desirable number of filters and corresponding openings, provided that the diameter of a cross section of light path 24 does not impinge upon a plurality of filters in a single casing due to the filters having been made to small. In addition, a single opening can be used to provide a passageway for light traversing more than one filter by sizing the opening large enough to encompass the area covered by the filters. Indeed, the housing can even be substantially semi-cylindrical, with filters embedded with in the wall formed by the semi-housing and the open "half" of the housing being equivalent to the openings 146 in Figure 8.

The apparatus and methods of the present invention are typically used, and the methods are typically performed, on living animals, preferably human patients. The apparatus and methods can also be used post-mortem, if desired. Thus, the illumination light is transmitted and the fluorescence, or other return light, is collected *in vivo*.

Turning to some alternative embodiments of the invention, in one such embodiment the emanating light from the target tissue can be directed into an optical beam splitter that divides the light into two or more beams and/or spectral regions of interest. The multiple beams and/or spectrally separated components are then each directed to discrete viewers, such as the different lenses of a binocular viewer.

In another embodiment of the invention, where the *in vivo* optical viewer is an endoscope, the distal end of the endoscope comprises a bioptome, which bioptome is preferably extensible and retractable. *See* U.S. Patent

Light Sources

The present invention can use any light source that provides a light that illuminates a target tissue. In one preferred embodiment, the illumination light induces fluorescence in the target tissue. For some aspects of the invention, the light source need not induce fluorescence, but may instead cause reflectance or other light to return from the target tissue. Selection of an appropriate light source is well within the ordinary skill in the art in view of the present specification. With regard to light sources that induce fluorescence, the light source can be selected to provide light from ultraviolet (UV) through visible light. Preferably, the light comprises green, blue or near-UV light. Also preferably, the light does not comprise UV light because such light can induce cancer or other problems within the patient organism, which is preferably a human being. Further preferably, the light consists essentially of blue light and/or green light.

Some examples of preferred light sources to generate the required excitation energy include a pulsed xenon flashlamp equipped with wavelength selection filters (Figure 10), a CW (continuous wave) mercury or xenon arc lamp equipped with wavelength selection filters (Figures 11 and 12), a Blue or UV CW laser, and a Blue or UV pulsed laser. These are discussed below. The light sources in these figures preferably have an indexed mechanical coupling adapter 82 moveably attached to an optically transmissive base 80 to move a waveguide 84 transverse with respect to a light path 24. The indexed mechanical coupling adapter ensures that the illumination waveguide 84 is positioned to maximize the amount of light entering the illumination waveguide 84, and can be controlled by system software, which controls pulse timing of the arc lamp power supply. Suitable indexed mechanical coupling adapters 82 are known in the art.

In Figure 10, a pulsed xenon flashlamp 70 comprises a sealed housing arc lamp 71 and power supply (not shown). The arc lamp 71 typically has an arc length of less than 2 mm and is optionally equipped with an integral reflector to maximize energy directed toward the illumination light guide of the endoscope, catheter or other optical probe. An optical filter or series of filters, such as a blocking filter 72 and wavelength selection filter 76 placed in the optical path, can select the wavelength of the illumination light. The energy emitted by the arc lamp is collected and focused by a focusing lens 78. A collimating lens 74 can be placed between the filters if desired to direct the light from the arc lamp 71 along a common path. In a preferred embodiment suitable

software program control. Wavelength selection can be accomplished by using a dye laser pumped by a shorter wavelength laser wherein wavelength selection is a function of dye characteristics and cavity monochrometer tuning. Alternatively, a longer wavelength laser equipped with a frequency doubling system and/or an optical parametric oscillator (OPO) can be used. The energy emitted by the laser is collected and focused by a lens system. The lenses are selected to direct the energy into the illumination light guide in a converging cone with an apex angle that is less than or equal to the acceptance angle defined by the numerical aperture of the illumination light guide.

Turning to another embodiment, Figure 13 is a schematic diagram showing a system wherein the light is emitted by a distally-located blue LED 170, which light is collimated by a collimating microlens 171 and then filtered by a short pass filter 172 to transmit the illumination to the skin for fluorescence excitation. Figure 14 is a schematic diagram showing light from a distally-located LED that can be other than a blue LED, and thus lacking short pass filter 172 which could be incompatible with the light emitted by a given LED (of course, other filters, such as long pass filters or band pass filters, can be placed in the position of short pass filter 172 if desired). Multiple LEDs can be used in order to increase the illumination power and/or provide multiple wavelengths of illumination light. Thus, a blue LED, a green LED, and a red LED can be used to provide full spectral illumination for reflectance measurements or other desired measurements, such as Raman responses.

Figure 15 shows one desired arrangement of the LEDs 170 (specifically identified by reference numbers 170a-170f) relative to the collection fiber 173 wherein the LEDs are located at the distal end of a probe. Figure 16 is a schematic diagram showing an LED assembly wherein the LEDs 170 are slightly tilted toward each other and a collection fiber 80 at the distal end 52 of an optical probe 6 and co-centered at a central point of a potential skin disease site 8. This arrangement enhances the ability of the LEDs to illuminate the same area of potential skin disease site 8.

Light Filters

The present invention can use any light filter that provides the selection and attenuation of light discussed herein. The making of such filters can be done using methods well known in the art and can be obtained, provided the desired requirements are set forth, for example, from Melles-Griot, Irvine,

CLAIMS

What is claimed is:

1. An endoscope for directly transmitting an image from an in vivo target tissue to a user, the endoscope comprising:

a body including a proximal end and a distal end, the body being configured to position the distal end proximate to the target tissue;

a light emitter proximate to the distal end to direct an illumination light to the target tissue;

an eyepiece ocular coupled to the body at the proximal end that is sized to fit a human eye;

at least one collection light guide including a collector to receive emanating light from the target tissue and a conductor to conduct the emanating light along at least a portion of a light path to the eyepiece ocular;

a wavelength selection filter aligned with the collection light guide to be disposed in the light path, the wavelength selection filter selectively transmitting at least two desired wavelength bands of the emanating light; and

a wavelength ratio scaling filter aligned with the collection light guide to be disposed in the light path, the wavelength ratio scaling filter selectively controlling the intensity of at least one of the desired wavelength bands, the wavelength selection filter and the wavelength ratio scaling filter manipulating the emanating light from the target tissue to selectively enhance an image of the target tissue.

2. The endoscope of claim 1 wherein the collection light guide transmits the emanating light to the eyepiece, wherein the user is able to directly view the target tissue directly through the eyepiece ocular without a transduction imaging device between the target tissue and the user.

3. The endoscope of claim 2 wherein the illumination light is conducted from a light source maintained at the proximal end of the endoscope to the light emitter at the distal end to of the endoscope via an illumination light guide.

4. The endoscope of claim 3 wherein the light emitter is a distal end of the illumination light guide.

14. The endoscope of claim 2 wherein one of the desired wavelength bands it green light and the wavelength ratio scaling filter is able to selectively vary the level of intensity of green light.

15. The endoscope of claim 9 wherein the long pass filter is maintained upstream from the collection light guide which is maintained upstream from the wavelength selection filter which is maintained upstream from the wavelength ratio scaling filter.

16. The endoscope of claim 2 wherein the endoscope is a surgical microscope.

17. The endoscope of claim 2 wherein the endoscope is a laparoscope.

18. The endoscope of claim 2 wherein the endoscope is a colposcope.

19. The endoscope of claim 2 wherein the wavelength selection filter blocks at least wavelengths of light that are within the overlapping photoreceptor response ranges of the human eye.

20. The endoscope of claim 2 wherein the wavelength ratio scaling filter is variable.

21. The endoscope of claim 20 wherein the wavelength ratio scaling filter is continuously variable.

22. An endoscope for directly transmitting an image from a target tissue to a user, the endoscope comprising:

a body including a proximal end and a distal end, the body being configured to position the distal end proximate to the target tissue;

means for emitting an illumination light from a location of the body at least proximate to the distal end;

means for collecting and conducting an emanating light from the target tissue along a light path to an eyepiece sized to fit a human eye at the proximal end,

27. The method of claim 23 wherein the illumination light is transmitted through a band pass filter maintained at the distal end of the endoscope, wherein the band pass filter transmits a selected wavelength band of light and blocks other light.

28. The method of claim 27 wherein the selected wavelength band is blue light able to induce fluorescence in the target tissue.

29. The method of claim 23 wherein the illumination light emitted from the light emitter consists essentially of a selected wavelength band and the light collection system further comprises a long pass filter disposed in the light path, wherein the long pass filter blocks light having about the same wavelength as the selected wavelength band and transmits other light.

30. The method of claim 27 wherein the illumination light emitted from the light emitter consists essentially of a selected wavelength band and the light collection system further comprises a long pass filter disposed in the light path, wherein the long pass filter blocks light having about the same wavelength as the selected wavelength band and transmits other light.

31. The method of claim 23 wherein the wavelength selection filter is maintained upstream in the light path from the wavelength ratio scaling filter.

32. The method of claim 23 wherein the long pass filter is maintained upstream in the light path from the wavelength selection filter and the wavelength ratio scaling filter.

33. The method of claim 23 wherein one of the desired wavelength band is green light and the wavelength ratio scaling filter is able to selectively vary the level of intensity of green light.

34. The method of claim 25 wherein the long pass filter is maintained upstream from the collection light guide which is maintained upstream from the wavelength selection filter which is maintained upstream from the wavelength ratio scaling filter.

wavelength bands of the emanating light, and a wavelength ratio scaling filter disposed in the light path and able to selectively control the intensity of at least one of the desired wavelength bands, and wherein the user is able to directly view the target tissue through the eyepiece ocular without an imaging device between the target tissue and the user.

39. The endoscope of claim 38 wherein the illumination light is conducted from a light source maintained at the proximal end of the endoscope to the light emitter at the distal end of the endoscope via the illumination light guide, and wherein a band pass filter that transmits substantially only blue light is disposed at the distal end of the illumination light guide.

40. The endoscope of claim 38 wherein the light emitter comprises a light source disposed at the distal end of the endoscope.

41. A filter assembly for a scope to transmit an image from an *in vivo* target tissue to a user, comprising:

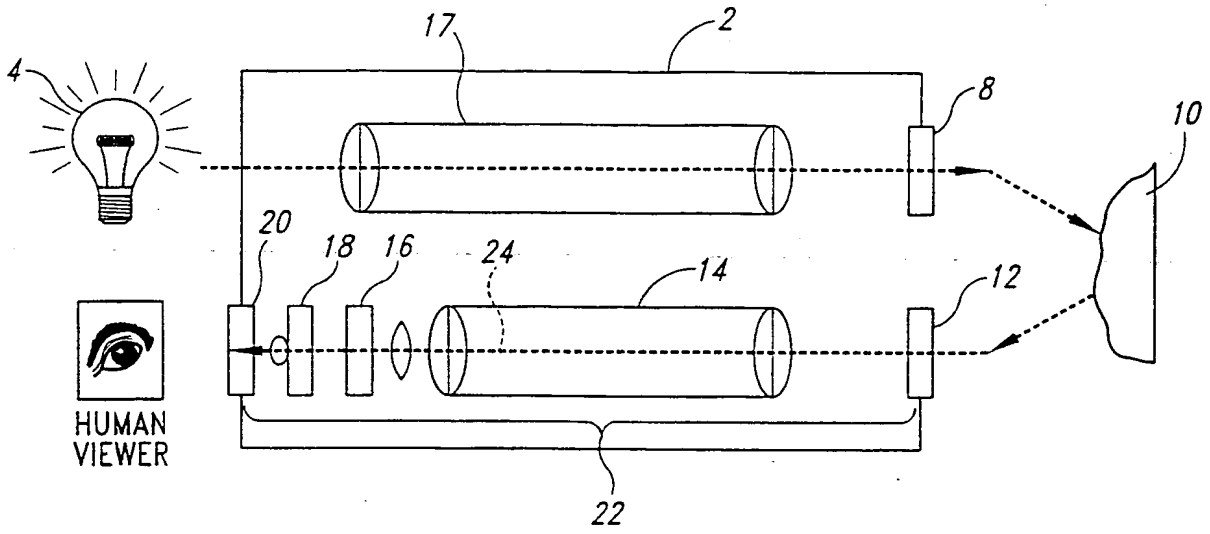
a casing including a proximal end with a first opening to receive a proximal section of the scope, a distal end with a second opening to receive a distal section of the scope, and a transmission passage extending between the first and second openings, the transmission passage being configured to transmit light along a light path from the distal end to the proximal end of the casing;

a rotatable housing attached to the casing, the rotatable housing including a knob configured to be gripped by a user and a filter holder positioned in the casing, the filter holder having at least one window; and

at least one filter received in the at least one window, the housing rotating within the casing to position the at least one filter in alignment with the light path for selectively enhancing an image of the target tissue.

42. The filter assembly of claim 41 wherein at least one of the filters disposed within the at least one wall of the filter assembly is able to transmit at least two discrete desired wavelength bands of the light.

43. The filter assembly of claim 42 wherein the filter assembly comprises at least two of the housings, at least one housing having a wavelength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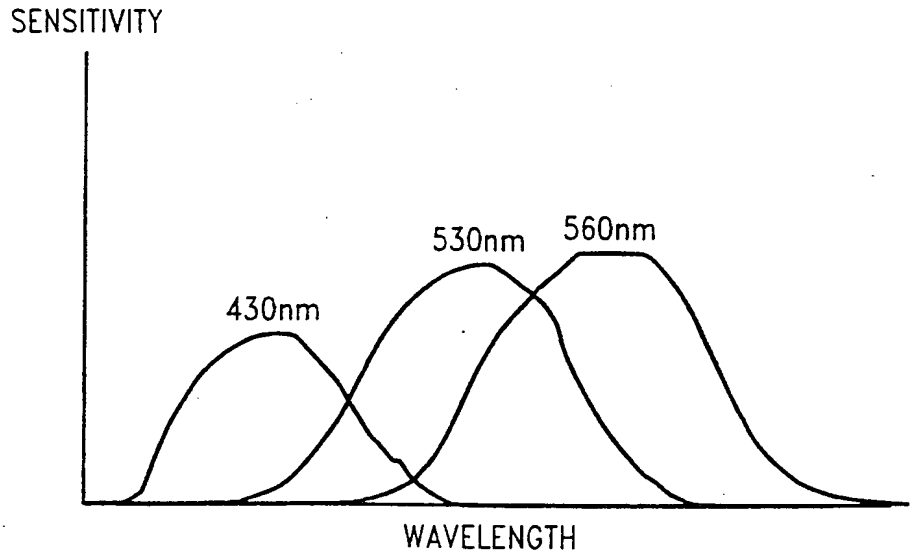
18
16
24
14
12
HUMAN
VIEWER
22

Fig. 1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430nm
WAVELENGTH

Fig. 2

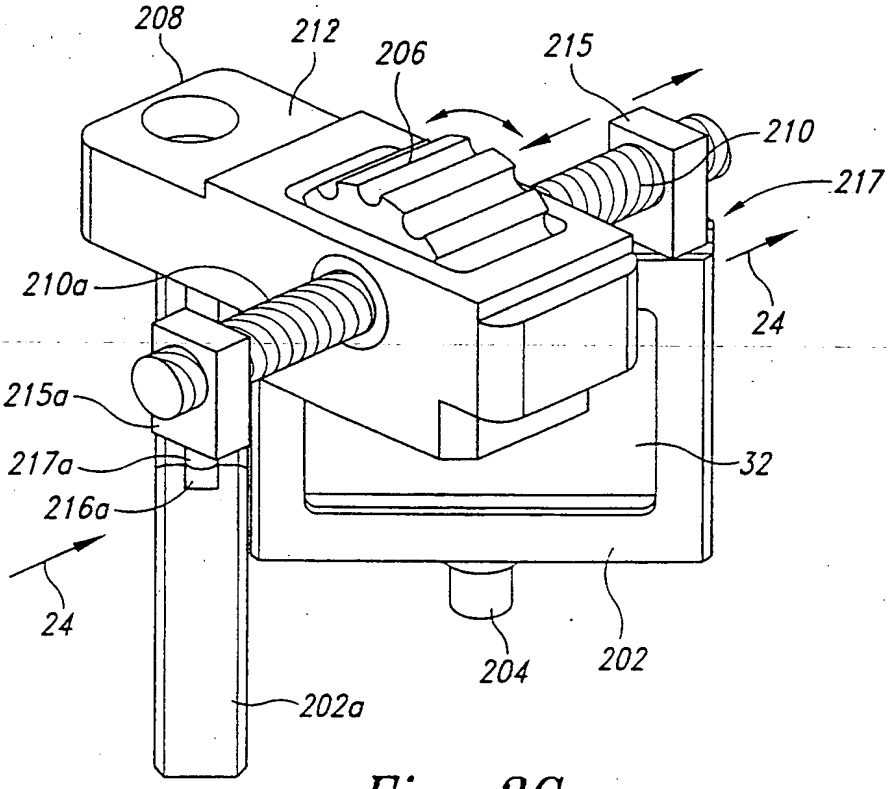
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Fig. 3C

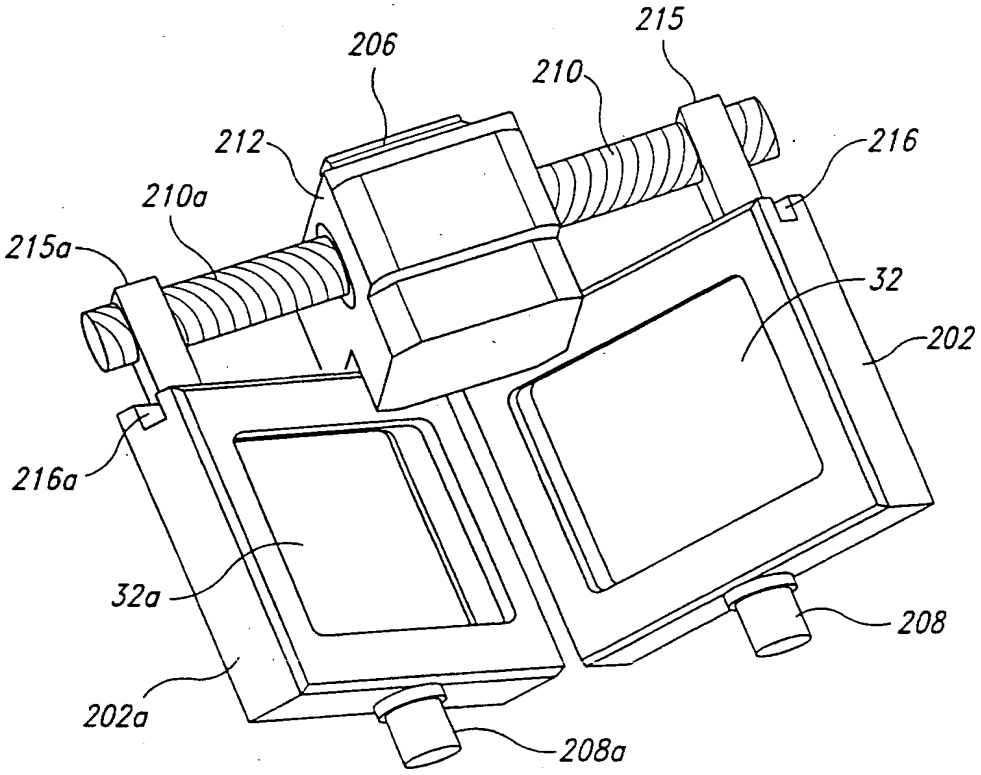
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Fig. 3D

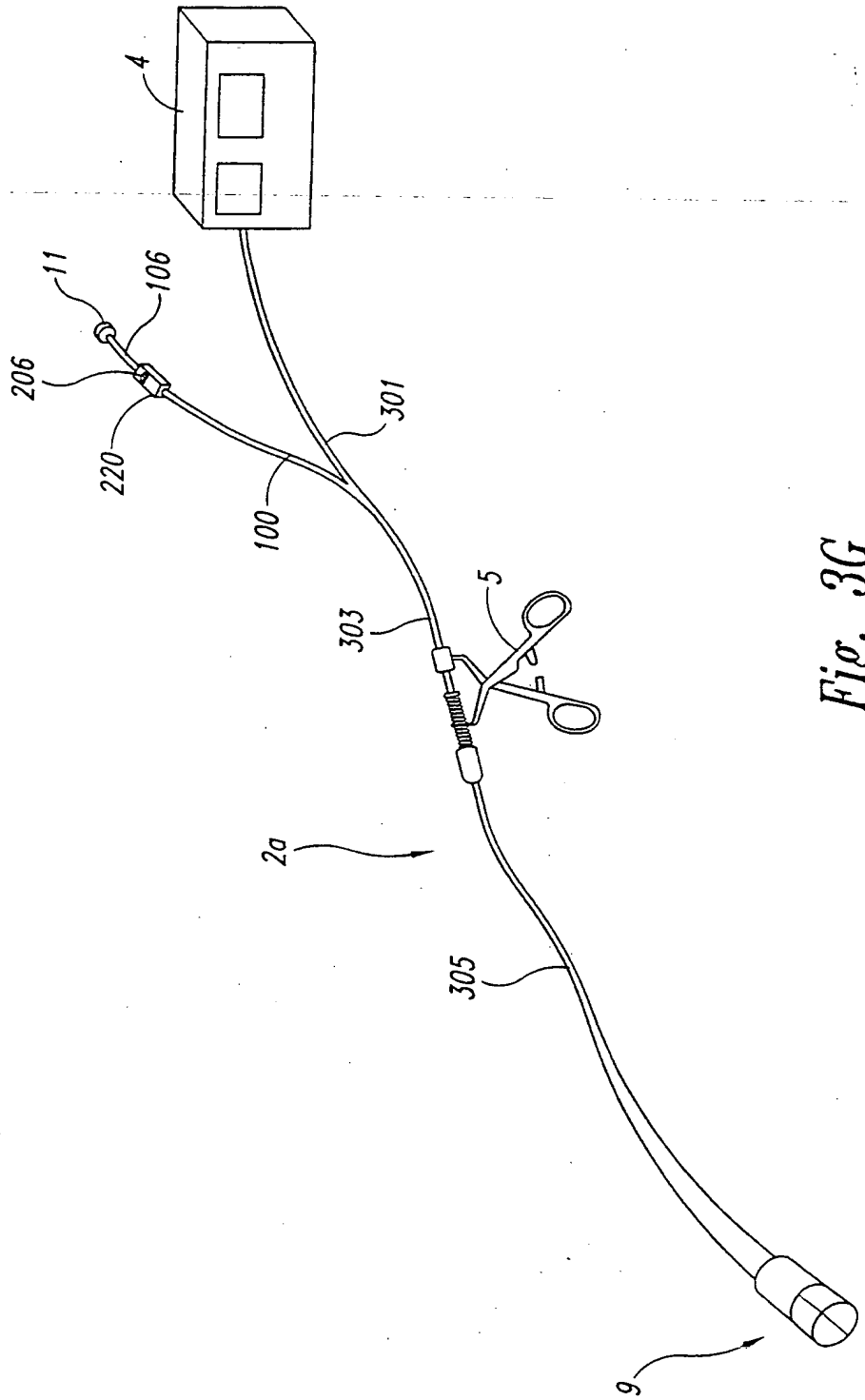

Fig. 3G

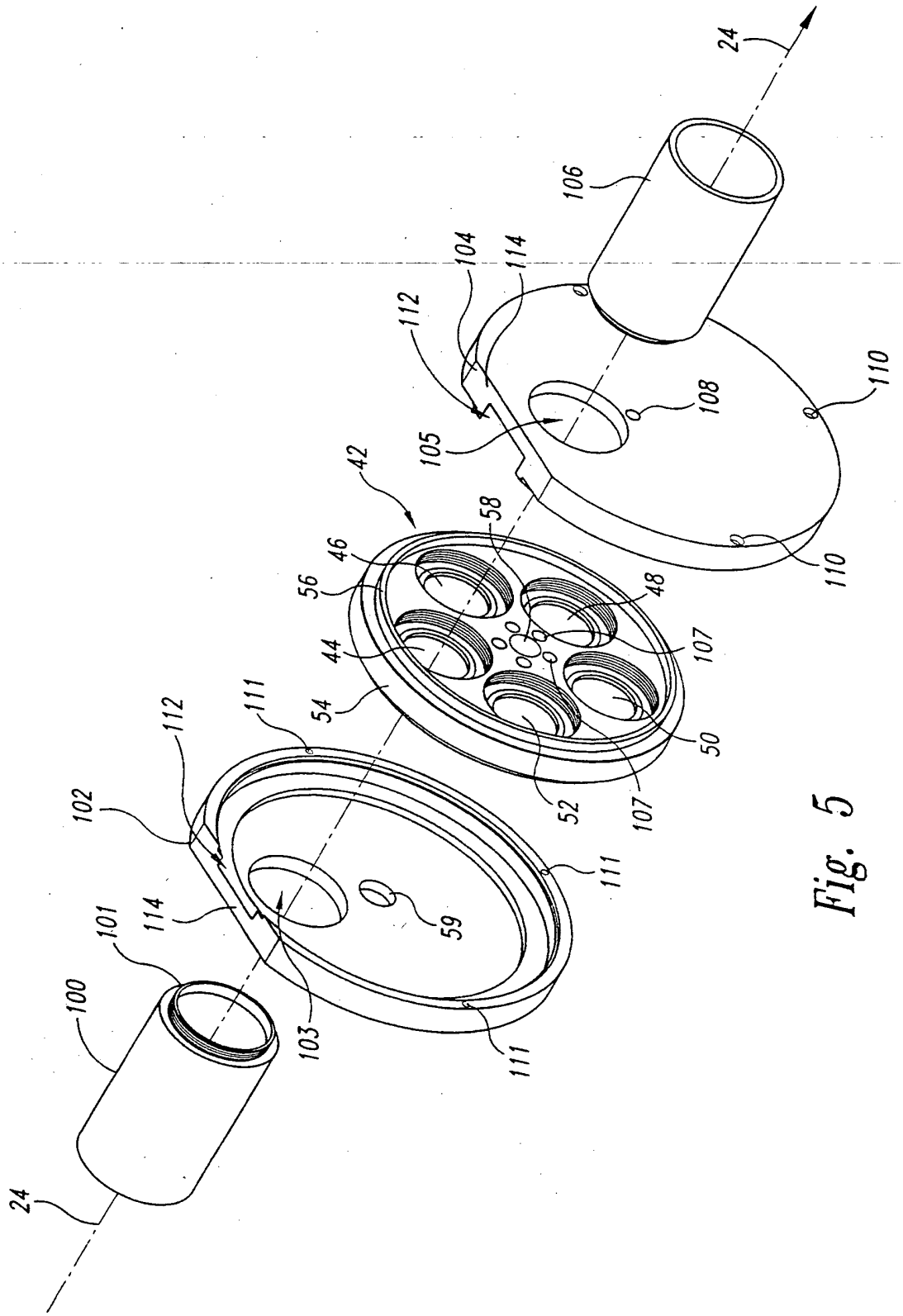
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Fig. 5

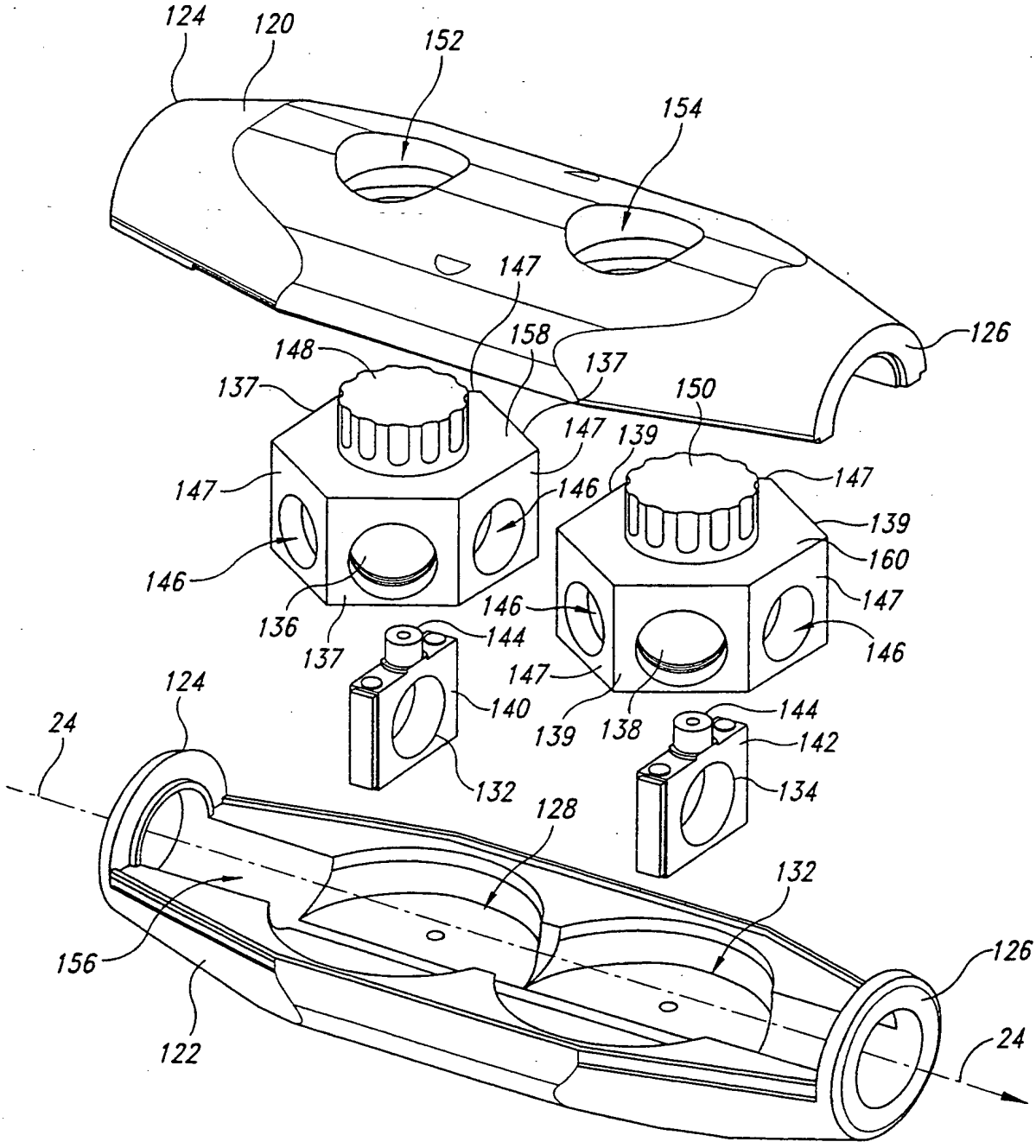
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Fig. 8

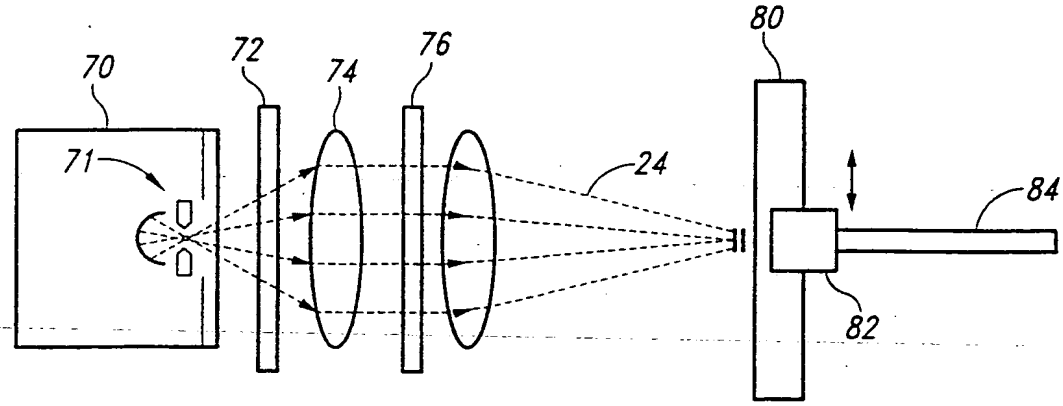

Fig. 10

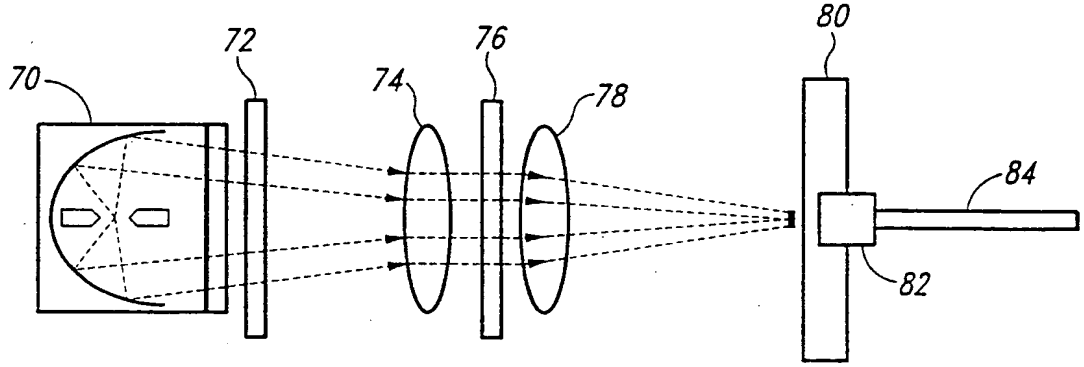

Fig. 11

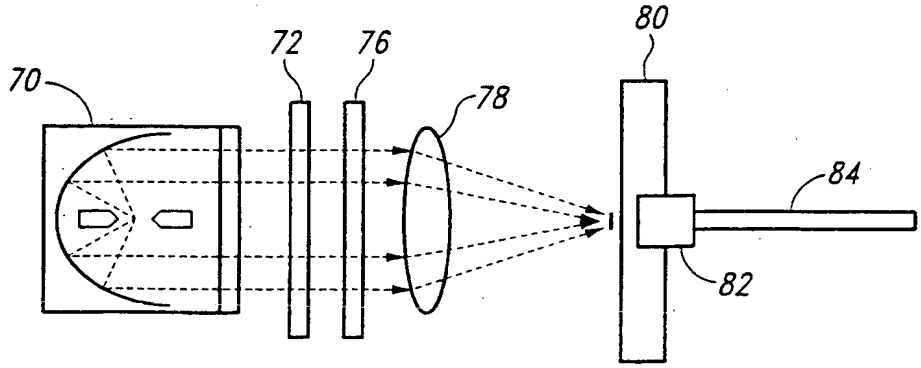

Fig. 12

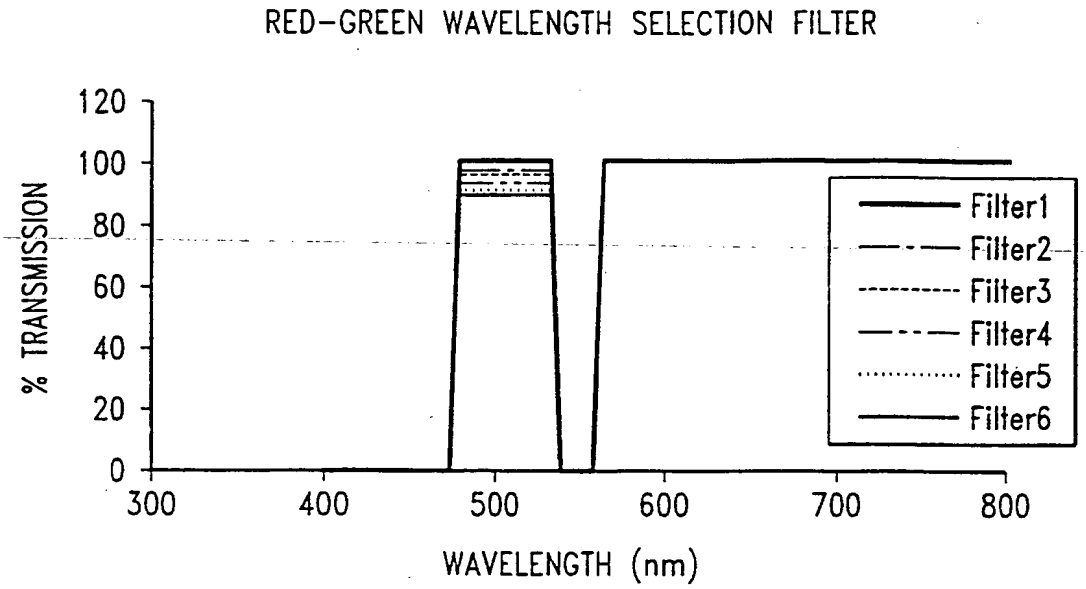

Fig. 17A

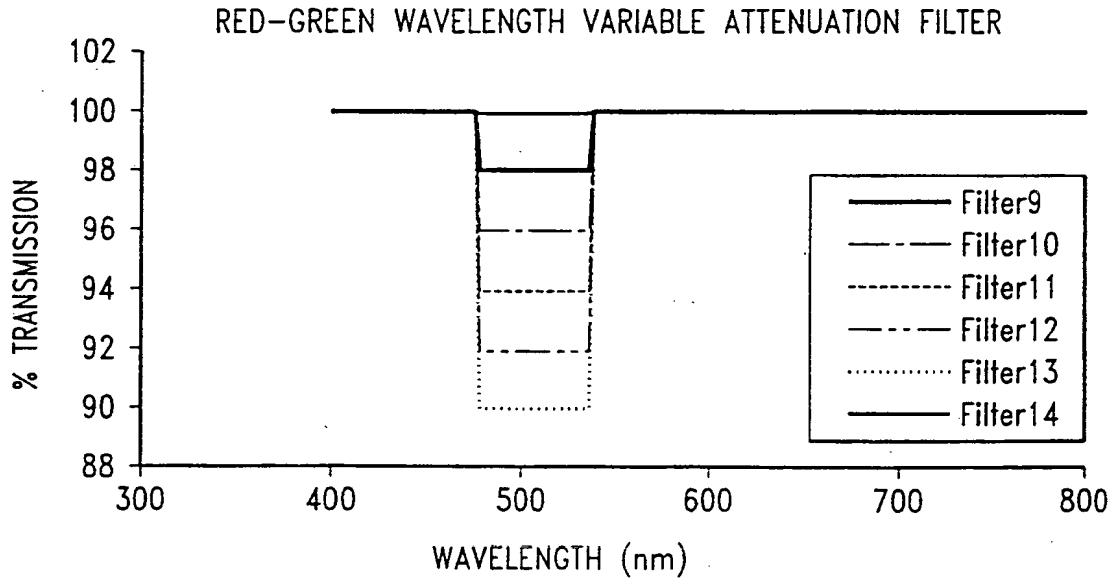

Fig. 17B

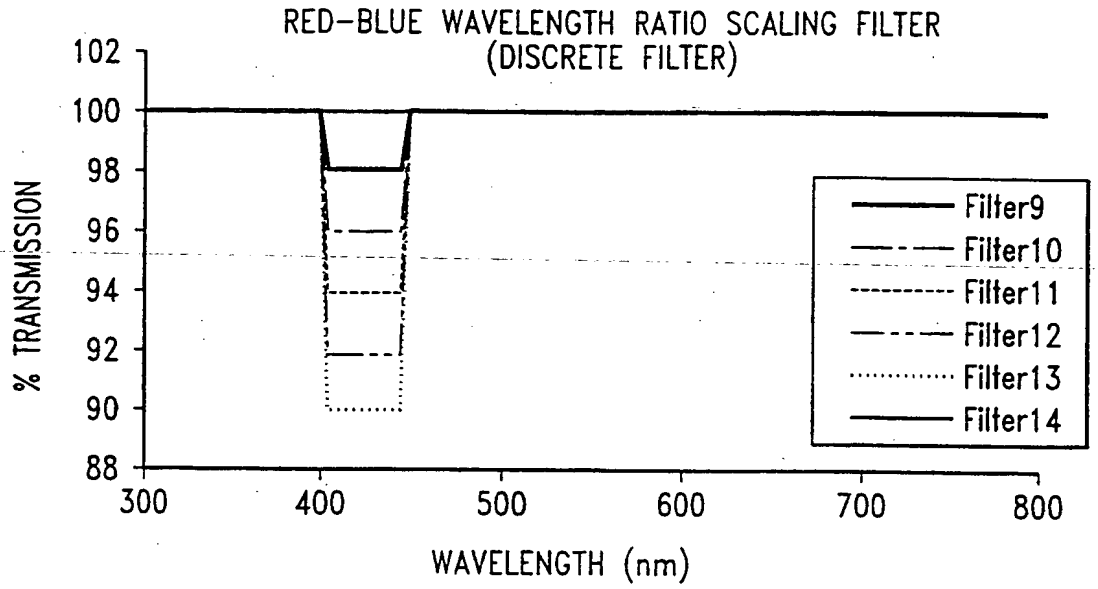

Fig. 18B

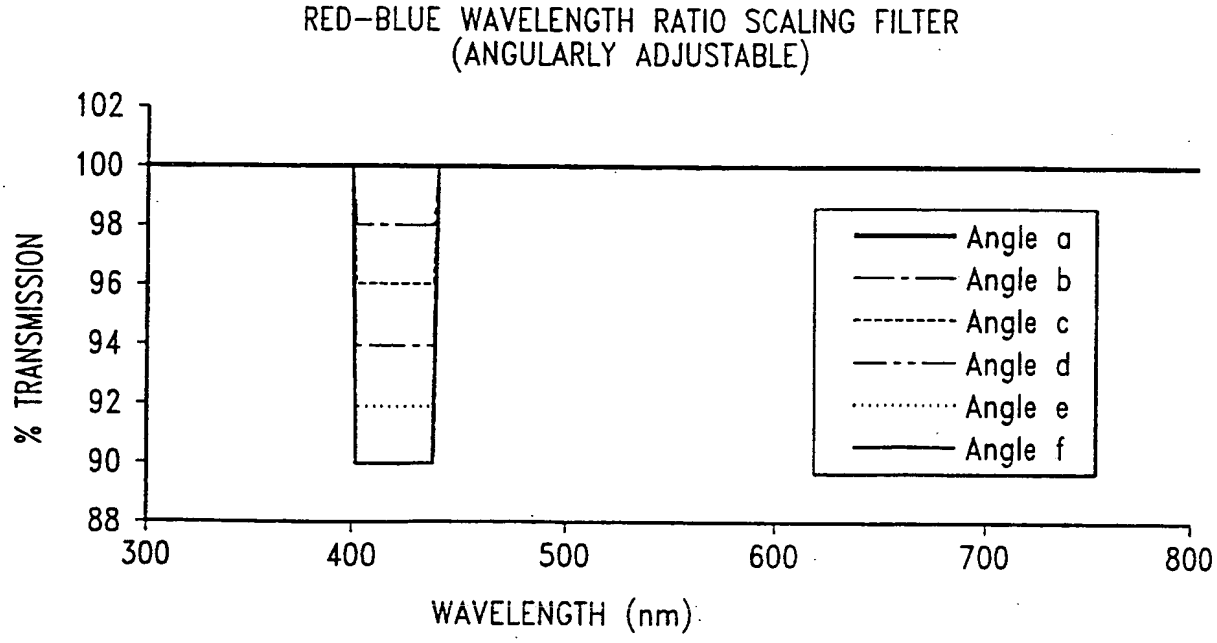

Fig. 18C

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information on patent family members

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